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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/600,182	06/20/2003	Fritz H. Bach	13681-012001	8996
26161	7590	10/19/2007		
FISH & RICHARDSON PC P.O. BOX 1022 MINNEAPOLIS, MN 55440-1022			EXAMINER SAUCIER, SANDRA E	
			ART UNIT 1651	PAPER NUMBER
			MAIL DATE 10/19/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/600,182	Applicant(s) BACH ET AL.	
	Examiner Sandra Saucier	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16-20 and 24-45 is/are pending in the application.
- 4a) Of the above claim(s) 16 and 17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 18-20 and 24-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>10/2/07, 9/13/07</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 16-20, 24-45 are pending and claims 18-20, 24-45 are considered on the merits.

The indication of allowable subject matter in the office action of 1/11/07 has been rescinded and examination proceeds on the elected invention.

Election/Restriction

Applicant's election with traverse of Group III in the reply filed on 8/1/07 is acknowledged. The traversal is on the grounds that all groups are related. This is not found persuasive because the patient to whom the treatment is administered is distinct. A donor in a transplantation method is not the same as the recipient nor is it the same as treating the organ *ex vivo*. Also, the examination of multiple inventions present burden because the prior art applicable to one invention would not likely be applicable to another invention and the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112

NEW MATTER

Claims 30-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Insertion of the limitation "nitric oxide and *the second treatment* are administered to the recipient within 1 to 20 days after transplantation" has no support in the as-filed specification. The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limitations which would show possession of the concept of these time ranges with any and all second treatment protocol. The specification states on page 27-28 that NO and CO can be administered starting immediately after the procedure and continuing for various periods of time. This is not the same as the instantly claimed limitations in claims 30-33. Further, there is no support found in the as-filed specification for the recitation of "live donor", or "brain-dead donor" in claims 35, 36. Nor is there support for the recitation of "upon determination that the transplanted organ is undergoing or about to undergo chronic rejection", in claim 34.

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This is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertions as detailed above are considered to be the insertion of new matter for the above reasons.

INDEFINITE

Claims 18-20, 24-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants have chosen "organs" as the elected species. However, on page 36 of the specification, applicant defines "organ" in opposition to art accepted definition to include tissues and cells, even a single cell. Thus, there is confusion regarding these terms. Although applicant may be their own lexicographer, there is no need to complicate matters by confusing the well-known distinctions in science and medicine that exist between organs, tissues and cells. In short, an organ is a differentiated structural and functional unit which is designed for some particular function and which consists of at least one tissue and may have many different tissues as components; a tissue is collection of a particular kind of cell aggregated with intercellular substance; cell is small mass of protoplasm which has a boundary or a membrane, see art accepted definitions supplied [U].

ENABLEMENT

Claims 18-20, 24-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the transplantation of any organ with administration of CO and NO. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The invention, in one embodiment, is directed to the transplantation of organs, which is the elected species. This term is interpreted in the common scientific sense of a differentiated structure composed of tissues and cells.

The claims encompass the transplantation of any organ with the treatment of the donor with CO and NO.

There is no working example directed to transplantation of any organ.

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The working example is directed to a cell culture treatment of isolated hepatocytes or to protection against acute liver failure induced by TNF- α /D-gal. This is a model of fulminant hepatic failure (hepatitis). Even for this model, no concomitant administration of CO and NO is demonstrated. Rather it appears that CO administration is equivalent to NO administration. In any case, no art accepted transplantation model is presented which demonstrates superior survival of transplanted livers when CO with NO is administered to the recipient.

Also, the state of the prior art regarding the transplantation of an organ such as a whole brain, for example is nonexistent.

Also, with regard to liver transplantation, no accepted animal model has been presented for treatment during the transplantation of liver. See Bishop *et al.* [V] where it is taught that liver has a better transplantation rate in rodents even when mismatched unlike other organs such as heart. Thus, liver is an organ which exhibits a less stringent matching requirement than other organs. Kanoria *et al.* [W] also discuss models for liver transplantation which include global ischemia. No art accepted animal model for liver transplantation has been used in the exemplification which clearly demonstrates efficacy of the treatment. Because liver may one of the most forgiving organs to transplant and no art accepted animal model for liver transplantation is presented, it is not reasonable to further predict that any and all patients receiving any organ can benefit from the treatment of the claimed method prior to, during or after transplantation.

Pharmaceutical therapies are unpredictable for the following reasons: (1) therapeutic compositions may be inactivated before producing an effect; (2) the therapeutic composition may not reach the target area; (3) other functional properties, known or unknown, may make the therapeutic composition unsuitable for *in vivo* therapeutic use. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. App. & Inter. 1992).

Also, there is unpredictability in the art of administering CO in order to enhance the transplantation of organs such as liver, as evidenced by applicants' own published documents, see Calabrese *et al.* [C9] where CO administered to donor pigs prevents apoptotic events in the renal xenotransplantation model, but this treatment does not extend the survival of the graft, Cozzi *et al.* [C15].

There is a body of literature which states that NO induces heme

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oxygenase-1, and that induction of heme oxygenase is the mechanism for the production of cellular CO, and that CO administration may have some benefits in some transplantation models, Otterbein *et al.* [C44], Hartsfield *et al.* [C23]. However, there is no evidence in the present application that NO and CO administration together produce synergistic results in an animal model of transplantation.

Although the specification discloses methods of administration of NO and CO *in vitro*, there are no data on the effectiveness of CO and NO administered to a transplant recipient and used in a therapeutic treatment of liver injury due to ischemia, reperfusion and immunogenicity which are some of the types of injury which occur during and after transplantation of a liver. Therefore, in view of the nature of the invention, the state of the prior art, the amount of guidance present in the specification and the breadth of the claims, it would take undue experimentation to practice the claimed invention.

As set forth in *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA) 1970: [Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of the enablement varies inversely with the degree of unpredictability of the factors involved. *Ex parte Humphreys*, 24 USPQ2d, 1260.

Conclusion

Applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). It is applicants' burden to indicate how amendments are supported by the ORIGINAL disclosure. Due to the procedure outlined in MPEP 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 USC 102 or 35 USC 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to the office action.

Any inquiry concerning this communication or earlier communications

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from the examiner should be directed to Sandra Saucier whose telephone number is (571) 272-0922. The examiner can normally be reached on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, M. Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Sandra Saucier
Primary Examiner
Art Unit 1651
October 11, 2007